Risk Analysis, Vol. 18, No. 1, 1998

Air Nicotine and Saliva Cotinine as Indicators of Workplace Passive Smoking Exposure and Risk[1]

James L. Repace,[2,7] Jennifer Jinot,[3] Steven Bayard,[3,6] Karen Emmons,[4] and S. Katharine Hammond[5]

Received November 19, 1996; revised August 22, 1997

We model nicotine from environmental tobacco smoke (ETS) in office air and salivary cotinine in nonsmoking U.S. workers. We estimate that: an average salivary cotinine level of 0.4 ng/ml corresponds to an increased lifetime mortality risk of 1/1000 for lung cancer, and 1/100 for heart disease; >95% of ETS-exposed office workers exceed OSHA's significant risk level for heart disease mortality, and 60% exceed significant risk for lung cancer mortality; 4000 heart disease deaths and 400 lung cancer deaths occur annually among office workers from passive smoking in the workplace, at the current 28% prevalence of unrestricted smoking in the office workplace.

KEY WORDS: Salivary cotinine; environmental tobacco smoke; air nicotine; Monte Carlo modeling; passive smoking; workplace; lung cancer; heart disease; risk assessment.

1. INTRODUCTION

A body of evidence on the health risks of environmental tobacco smoke (ETS) has accumulated during the past two decades,[1,2,10,32,67,68] connecting exposure to ETS to the risk of mortality. The U.S. Environmental Protection Agency (EPA) declared ETS to be a known human lung carcinogen.[1] The American Heart Association proclaimed passive smoking to be a cause of fatal cardiovascular disease in nonsmokers.[32] The U.S. Occupational Safety and Health Administration (OSHA), citing the risk of heart and lung fatality to nonsmoking workers from passive smoking, has proposed a rule to eliminate nonsmokers' ETS exposures in the workplace.[2,68] In a protracted and contentious public hearing on this proposed rule in 1994–1995, the tobacco industry challenged OSHA's proposal, asserting that ETS exposures in the workplace were low, and that any possible risks were less than the "significant risk" level which the Supreme Court imposed as a test to justify OSHA regulation, and therefore were legally insufficient to allow OSHA to act.[33]

In order to estimate the levels and significance of workplace ETS exposure and dose on nonsmokers, this paper seeks to (1) develop a physical model to predict office nicotine concentrations from workplace smoking; (2) develop a pharmacokinetic model to predict salivary cotinine levels in nonsmoking workers due to passive smoking; (3) develop expected frequency distributions for modeled exposure and dose, and compare these respectively with an observed distribution of nicotine in

[1] Disclaimer: The views expressed are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA or OSHA. The U.S. Government has the right to retain an exclusive royalty-free license to any copyright covering this article.

[2] Office of Air and Radiation, U.S. Environmental Protection Agency, Washington, DC 20460

[3] Office of Research & Development, U.S. Environmental Protection Agency, Washington, DC 20460

[4] Dana-Farber Cancer Institute, Harvard School of Public Health, Boston, MA 02115

[5] School of Public Health, University of California, Berkeley, Berkeley, CA 94720

[6] Present Address: Health Standards Division, OSHA, U.S. Dept. of Labor, Washington, DC 20210.

[7] Address all correspondence to: J. L. Repace at 101 Felicia Lane, Bowie, MD 20720. Email:⟨repace@erols.com⟩ This work was performed in his private capacity.

0272-4332/98/0200-0071$15.00/1

office workplace air and an observed salivary cotinine distribution from workers exposed to ETS only at work; (4) develop exposure– and dose–response relationships between airborne nicotine and salivary cotinine and the risk of ETS-induced lung cancer and heart disease; and (5) estimate the magnitude of mortality from ETS exposure for workers in office workplaces with unrestricted smoking.

Nicotine and its primary metabolite cotinine are good indicators of ETS exposure in nonsmokers.[10,39,40,67] Airborne nicotine has been found to be highly correlated to the number of cigarettes smoked in the presence of nonsmokers and to urinary cotinine in those nonsmokers.[3,9,61] During passive smoking, nonsmokers inhale nicotine proportionally to the product of concentration, exposure duration, and respiration rate.[18,37,53] Inhaled nicotine is absorbed into the bloodsteam through the lung, and is rapidly and extensively metabolized with a half-life of the order of 2 hrs by the liver into cotinine and nicotine N-oxide.[40] The intake of nicotine reflects exposure to other constituents of ETS.[39] In nonsmokers, cotinine has a half-life in plasma on the order of 17 hrs,[39] and thus is an indicator of the integrated exposure to ETS over the previous 1–2 days.[3,39] Cotinine appears in all body fluids and on average is excreted in fixed relationships from plasma (i.e., serum) into saliva and urine.[11,12,39] Salivary cotinine accurately differentiates current smokers from nonsmokers in field settings such as worksites, and a cutoff of 10 ng/ml is useful in differentiating ETS-exposed nonsmokers from light smokers.[38] Although nicotine is present in trace amounts in certain vegetables, dietary sources are negligible compared to passive smoking as a contribution to body fluid cotinine,[13,14,34,39] arguments to the contrary[49] notwithstanding. Thus, cotinine in body fluids provides a valid quantitative measure of recent integrated ETS exposure.[39,40]

Lung cancer and heart disease have been associated with workplace passive smoking. Lung cancer has been associated with U.S. workplace ETS exposure in the largest and best[1,2] case-control study of passive smoking (653 cases, 1253 controls).[20,26,55] A subset of this group (526 cases, 1148 controls), women who reported ever working outside the home for ≥6 months had an adjusted odds ratio of 1.58 (95% CI, 1.21–2.02) for exposed workers vs. nonexposed workers, for all lung cancer and for adenocarcinoma, controlling for numerous covariates and adult nonworkplace exposures.[55] For women with 30 or more years of work exposure, an odds ratio of 2.08 (95% CI, 1.35–3.20; $p < 0.001$) was found for lung cancer.[55] In a prospective study of coronary heart disease (CHD) in 32,000 female U.S. nurses aged 31–61 yrs, for nonsmoking women exposed only at work, a dose–response gradient for passive smoking and CHD was observed,[72] with adjusted relative risks of CHD being 1.00 [for no exposure], 1.58 (95% CI, 0.93–2.68) [occasional exposure], and 1.91 (95% CI, 1.11–3.28) [regular exposure]. The risks of CHD were similar among women exposed at home to those exposed only at work. A workplace CHD effect was also found in China.[44]

In addition, lung cancer and heart disease mortality have been associated with nonsmokers' cotinine levels. In an epidemiological case-control study of lung cancer (23 cases, 191 controls, 1989–1992), in a cohort of Netherlands women (n = 214) aged 40–64, lung cancer risk was found to be correlated with their historical urinary cotinine excretion measured from 1977–1991.[42] The average odds ratio for heavier passive smoking (urinary cotinine 9.2–100 ng/mg creatinine) to lighter passive smoking (urinary cotinine < 9.2 ng/mg creatinine) was 2.6 (95% CL, 0.75–8.7).[42] Tunstall-Pedoe *et al.*[54] in a Scottish cross-sectional study of passive smoking and heart disease in 786 men and 1492 women, found that increasing quantitative measures of serum cotinine in ng/ml correlated to diagnosed heart disease risk, with an odds ratio of 2.7 (95% CI, 1.3–5.6) for the highest vs. the lowest exposure quartile, adjusted for age, housing tenure, total cholesterol, and blood pressure.

In sum, lung cancer and heart disease have been associated with cotinine levels in nonsmokers as well as with passive smoking in the workplace; thus, it appears that air nicotine and cotinine in body fluids can be useful markers for estimating ETS exposure and dose and for assessing nonsmokers' risk of heart and lung mortality from passive smoking in the workplace.

2. FIELD STUDIES OF WORKPLACE AIR NICOTINE AND WORKERS' SALIVARY COTININE

Nicotine. In a 1991–1992 study of ETS nicotine in the air of 25 diverse worksites in central and eastern Massachusetts, sampled by Hammond *et al.*,[21] week-average passive nicotine monitors were deployed (15–25 samplers per worksite) and analyzed by nitrogen-sensitive gas chromatography, with a detection limit of 0 $\mu g/m^3$ over a 7 day sampling time. Shop and office locations were sampled separately. Companies were classified as to smoking policy: allowed throughout the worksite (11 worksites); restricted to designated areas (eight worksites); or banned throughout the worksite (six worksites). For 61 samples collected over a 7 day peri-

in the open offices located in nine office worksites where smoking was not restricted and occupancy consisted of mixed smokers and nonsmokers, the median nicotine concentration was 8.6 μg/m³, the mean value was 14.0 μg/m³, and the range was 0–130 μg/m³. Measured values were adjusted to a 9-hr workday (assuming 8 hrs of work plus 1 hr for lunch) and a 45 hr work-week. Nicotine values were approximately lognormally distributed, as is typical for pollutant concentrations in indoor air.[24]

Cotinine. Emmons *et al.*[15,57] measured saliva cotinine concentrations by GC-MS in 186 nonsmoking volunteers from Rhode Island in the late 1980s, and found that 83% had detectable values. These persons were 97% white, 63% female, and had completed an average of about 16 years of education (the majority were office workers; some worked in psychiatric hospitals and substance abuse clinics). Typical workdays were 7 hrs plus one hour for lunch. Subjects were questioned about ETS exposure at work and at home; no other exposures were considered. Eighty-four percent of those who worked outside the home (75.6% of the total sample) reported having regular exposure to smokers at work. Emmons *et al.*[15] found that the cotinine concentrations of the subjects were successfully predicted by a regression equation which included only the number of smokers at home and at work and the number of minutes of exposure recorded in a daily diary. Emmons *et al.*[15] reported that subjects who lived with smokers had median salivary cotinine levels of 1.0 ng/ml (range <0.5–7.4 ng/ml). Subjects who worked regularly with smokers had median cotinine levels of 0.8 ng/ml (range <0.5–7.4 ng/ml). Workplace nicotine levels were not measured. Means were not presented, because 17% of the subjects had cotinine levels below the limit of detection (0.5 ng/ml) which is well within the range of cotinine levels of interest.

3. MODEL DEVELOPMENT

We now derive point-estimate models relating the parameters of ETS generation, transport, and removal in the workplace to the mean values of airborne nicotine in workplace air and the corresponding salivary cotinine levels in workers.

Nicotine. Steady-state levels of nicotine [like respirable suspended particulate (RSP) and carbon monoxide (CO)] from ETS in an indoor space are directly proportional to the ETS source strength ($rG_N n_s$), where r is the smoking rate for the smoker (cigarettes per smoker-hour), G_N is the nicotine emission rate (micrograms per cigarette), and n_s is the number of smokers.[4,22,31] Steady-state levels are also inversely proportional to a dilution and removal factor (VqC_v), where V is the dilution volume (cubic meters) and qC_v is the effective air exchange rate (air changes per hour [ach]), which incorporates removal by ventilation, C_v, and an empirically determined factor, q, which increases C_v to account for ETS decay from absorption by surfaces (dimensionless).[4] For nonabsorptive gases like CO, q = 1, while for ETS constituents like nicotine, which decay by sorptive processes on surfaces, $q > 1$.[4] These factors are combined in the mass-balance model[5,6] to estimate the steady-state ETS-Nicotine concentration N (in units of micrograms per cubic meter)[4,22,31]:

$$N = (rG_N n_s/VqC_v) \quad (1)$$

The growth of the time-dependent nicotine concentration N(t) from the onset of smoking at $t = 0$ is given by:

$$N(t) = N(1 - e^{-tqC_v}) \quad (2)$$

and its decay following the cessation of smoking is given by (for $t \geq t_s$):

$$N(t) = N' e^{-tqC_v} \quad (3)$$

$$\text{where } N' = N(1 - e^{-t_s qC_v}) \quad (4)$$

and t_s is the duration of smoking. During the course of a normal 8-hr workday, workers are assumed to arrive at 9 am, work until 12 noon, go to lunch until 1 pm, then work until 5 pm. In this case, the office morning nicotine concentration will be described by Eq. (2), the concentration during the lunch hour by eq. (3), and the afternoon concentration by the sum of Eqs. (2) and (3). The 8-hr time-weighted workshift average nicotine concentration $N_{8\text{-TWA}}$ will then be given by the product fN, where f is a factor which converts the steady-state concentration to an 8-hr time-weighted average (Appendix), allowing for departures from equilibrium due to growth and decay processes associated with build-up of the concentration from zero in the AM, decay during lunch hour and beyond, and buildup in the PM, and is calculated from time-weighted integrals of Eq. (2) and (3). Accordingly, in units of μg/m³,

$$N_{8\text{-TWA}} = frG_N n_s/VqC_v \quad (5)$$

Cotinine. Repace and Lowrey's[3] pharmacokinetic model for cotinine in urine and plasma was found to predict mean values for cotinine in both these body fluids to within 10%–15% of the observed median values from clinical epidemiological studies, and values predicted for the most-exposed nonsmokers fell well within the range of cut-off values typically used by epidemiologists to differentiate heavy passive smokers from

Table I. Model Symbols, Definitions, Units, Range or Standard Deviation, and References for the Parameters in the Monte Carlo Simulation of Air Nicotine and Salivary Cotinine as a Function of Workplace and Biological Parameters as Calculated in the Following Elemental Simulation Equations;

$$N_{8\text{-TWA}}\ (\mu g/m^3) = (rfG_N P_s d_p/qC_v) \text{ and } S\ (ng/ml) = 1000\ (\gamma\phi\alpha\rho/\delta\tau)(H)(N_{8\text{-TWA}})$$

Symbol	Monte Carlo simulation parameter definitions and units	Target mean for simulation	Standard deviation and bounds used in simulation (bold values) vs. (range or std dev reported in reference for target mean)	Distribution type used in simulation[a]	Sample size and reference for target mean
α	lung nicotine absorption efficiency (dimensionless)	0.71	**0.21 SD bounds: 0.01–1.0** 0.10 SD, range: 0.45–0.95	TN	(n = 17)[47]
γ	salivary-to-plasma cotinine ratio (dimensionless)	1.16	**0.35 SD bounds: 0.10–3.0**	N	(n = 100)[12]
δ	plasma cotinine clearance, (ml/min)	61	**18 SD bounds: 20–100** 8.0 SD	N	(n = 13)[11,71]
ϕ	nicotine-to-cotinine conversion efficiency (dimensionless)	0.78	**0.16 SD bounds: 0.01–1.00** 0.10 SD range: 0.49–1.0	TN	(n = 146) (Appendix)
ρ	respiration rate (m^3/hr)	0.90	**0.18 SD bounds 0.4–1.4**	N	Ref. 48
τ	number of minutes per day	1440	dose is averaged over 1 day	—	—
C_v	air exchange rate (air changes per hour) (hr^{-1})	0.84	**0.42 SD bounds 0.2–8** 0.24 SD range: 0.1–3.3	LN	(n = 13 bldgs.)[25]
f	8-hr time-weighted averaging factor (dimensionless)		$f = \{7/8 + (-1 + e^{-4qC_v} - e^{-5qC_v} + e^{-8qC_v}) / 8qC_v\}$		(Appendix)
G_N	nicotine emissions per cigarette (µg/cig)	1800	**540 SD bounds 700–2900** 1762 ± 282 SD range: 1100–2600	N	(n = 50 brands)[27]
H	duration of exposure (hr/day)	7	**0.5 SD; bounds 6–8**	N	See text
d_p	Office person density (10-ft ceiling) (pers/m^3)	0.025	**0.005 SD bounds 0.005–0.08** range and SD not given	N	Ref. (7)
q	ratio of effective to ventilatory air exchange rate (dimensionless)	2.2	**0.33 SD bounds 1–4** range: 1–4	LN	Ref. 4 and 46 (Appendix)
r	cigarettes per smoker-hour	2	**0.60 SD bounds 0.1–6**	N	Ref. 4
P_s	smoking prevalence (dimensionless)	0.29	**0.06 SD bounds 0.05–0.9**	N	(n = 41,000)[34,69]

[a] N: normal, LN: lognormal, TN: truncated normal.

light active smokers.[16] This model may be extended to salivary cotinine as follows:

The daily average dose of ETS nicotine, D, in units of µg/day, absorbed by the lung into plasma is given[3] by the expression:

$$D = \alpha\ \rho H N_{ave} \tag{6}$$

where α is the absorption efficiency for inhaled nicotine, ρ is the nonsmoker's respiration rate during exposure in m^3/hr, H is the duration of exposure in hrs/day, and N_{ave} is the daily average nicotine concentration, which is given by Eq. (5).

The resultant mean plasma cotinine concentration, P, in units of µg/ml, is then given[3] by the expression:

$$P = \phi D/\delta\tau \tag{7}$$

where ϕ is the nicotine-to-cotinine conversion efficiency, δ is the nonsmokers' plasma cotinine clearance in ml/min, and τ is the length of a day in minutes. [Numerical values and references for all parameters are summarized in Table I]. Curvall et al.[11] and Jarvis[12] have shown that the saliva cotinine concentration (given here in units of µg/ml, but generally expressed in units of ng/ml) is proportional to the plasma cotinine concentration with a constant of proportionality which we define as γ:

$$S = \gamma P \tag{8}$$

By combining Eqs. (5–8) the following general expression for the estimated steady-state saliva cotinine concentration, S, is derived:

$$S = (\gamma\phi\alpha\rho/\delta\tau)(H)(frG_N n_s/VqC_v) \tag{9}$$

Equation 9 shows that saliva cotinine S is the product of three sets of parameters: physiological, exposure duration, and exposure concentration. While the phys

ological parameters γ, ϕ, α, ρ, and δ may vary considerably from individual to individual, in large numbers of subjects they will converge toward group means.

4. POINT-ESTIMATE MODEL PREDICTIONS AND VALIDATION

We now apply Eq. (5) to the case of the office workplace to generate point estimates of the workshift mean for the nicotine concentration, $N_{8\text{-TWA}}$, in a typical U.S. office workplace and Eq. (9) to estimate the resultant mean daily salivary cotinine concentration, S, expected for a typical nonsmoking worker in that workplace. The parameter values used are discussed in the Appendix and summarized in Table I.

Nicotine. For a 1000 ft² open plan office (a 10 ft ceiling is assumed), the ASHRAE Standard design occupancy will be seven persons,[7] and at a 1991 smoking prevalence of 29%,[23] this would yield two smokers. The design outdoor air supply rate recommended by the ASHRAE Standard for offices is 20 ft³ per minute per occupant (cfm/occ) (10 Lps/occ).[7] The equivalent air exchange rate due to ventilation is C_v = 20 cfm/occ × 60 min/hr × seven occupants / 10,000 ft³ = 0.84 air changes per hour. Using the values r = 2 cig/sm-hr,[4] q = 2.2,[4] G_N = 1800 µg/cfg (Appendix), V = 10,000 ft³ = 283 m³, and f = 0.81 (Appendix) in Eq. (5), we estimate an 8-hr time-weighted mean nicotine concentration $N_{8\text{-TWA}} = f r G_N n_s / V q C_v$ = 0.81 × 2 × 1800 × 2 / (283 × 2.2 × 0.84) = 11.2 µg/m³. This value may be compared with the observed values, adjusted to an 8-hr workshift, of 15.8 µg/m³ for the arithmetic mean, and 9.7 µg/m³ for the median, from data measured by Hammond *et al.*[21] for the open-plan workplaces as discussed above. Thus, by making reasonable assumptions for the constants and choosing average values for the workplace parameters, the model yields a point estimate between the median and the mean, in reasonable agreement with observations.

Cotinine. Similarly, we apply Eq. (9) directly to calculate S, using the same values of the parameters used to calculate $N_{8\text{-TWA}}$ above for the model office workplace. From the Appendix, ϕ = 0.78, γ = 1.16, α = 0.71, ρ = 0.9 m³/hr, and δ = 61 ml/min. We assume the workers are exposed to $N_{8\text{-TWA}}$ for H = 7 hrs, while τ = 1440 min, to calculate a daily average. Then the predicted mean salivary cotinine for a nonsmoker exposed to ETS in this office is $S = (\gamma\phi\alpha\rho/\delta\tau) \cdot (H) \cdot N_{8\text{-TWA}}$ = (1.16 × 0.78 × 0.71 × 0.9) / (61 × 1440) × 7 × (11.2) × 1000 ng/µg = 0.52 ng/ml. What do the observational data show? Emmons *et al.*'s subjects reporting exposure "at work only" had a median salivary cotinine value of 0.46 ng/ml for the 89 subjects.[15] The predicted mean yields a point estimate reasonably close to and higher than the median, as expected (the mean value was not reported due to a number of readings occurring below the limit of detection). The ratio S/N = 0.52 ng/ml/11.2 µg/m³ = 0.046. Thus, reasonable agreement between theory and experiment is achieved, suggesting that the model approximates reality. However, with a point estimate model, only the arithmetic mean of a distribution can be predicted for comparison with observations; using the probabilistic technique described below, the proposed models can be compared to the entire distributions of airborne nicotine and salivary cotinine observed in field studies.

5. MONTE CARLO SIMULATION AND PARAMETERS OF THE NICOTINE AND COTININE DISTRIBUTIONS

Assuming probability distributions for the model parameters instead of single values, it is possible to estimate distributions of nicotine and cotinine values by Monte Carlo simulation.[41] In the simulation, each individual parameter in Eqs. 5 and 9 is replaced by a distribution of values rather than a single mean value. For example, the physiological parameters γ, ϕ, α, ρ, and δ will differ for different individuals; the physical parameters of workplace exposure, such as C_v, will differ for different workplaces; and the emissions of different cigarettes will differ as a result of variations in product design as well as the way they are smoked, impacting on G_N. For some parameters in Eqs. (5) and (9), the shape of the distribution is assumed to be normal (e.g., the physiological coefficients), and in others lognormal (e.g., certain physical ones dealing with dilution phenomena[24] such as ventilation[25])—see the Appendix.

Table I lists the parameters and their assumed distributions. Parameter means are based upon reported or expected values; however, the range and standard deviations are increased in some cases (shown in bold type in Table I) to reflect greater variability and uncertainty in extrapolating parameter values derived from limited data to the more general scenario we are attempting to simulate, i.e., the distribution of nicotine levels in U.S. open office workplaces with unrestricted smoking, and the corresponding salivary cotinine levels in U.S. office workers. Using the reported standard deviations where available (primarily for the physiological parameters) did not materially affect the simulation results (results not shown). For other parameters, no data are available,

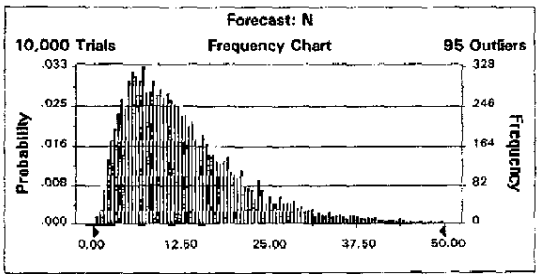

Fig. 1. Monte Carlo simulation of the expected nicotine frequency distribution in U.S. office workplaces with unrestricted smoking, generated from the physical model described in Eq. (5) using 10,000 random samples from the parameter distributions described in Table I. The median value is 11.3 μg/m³, the mean value is 13.8 μg/m³, and the range is 0.5–109 μg/m³.

Table II. Comparison of Simulated and Observed Nicotine $\{N_{8\text{-TWA}}\}$ and Cotinine $\{S\}$ Distributions by Exposure/Dose Percentile: The Air Nicotine Values Are Those Expected for an Office Workplace with Unrestricted Smoking and the Salivary Cotinine Levels Are Those Expected for Nonsmokers from Daily Passive Smoking in Those Office Workplaces

Concentration	Air nicotine (μg/m³)		Salivary cotinine (ng/ml)	
Percentile	Observed 8-hr TWA Hammond *et al.*[21] (n = 61)	Predicted 8-hr TWA (n = 10,000)	Observed Emmons *et al.*[15] (n = 89)	Predicted steady state (n = 10,000)
0	0.00	0.50	—	0.01
5	0.056	3.36	—	0.10
10	0.67	4.46	—	0.14
20	1.46	6.23	—	0.22
30	2.70	7.79	—	0.30
40	4.05	9.34	—	0.38[a]
50	9.67	11.25	0.5	0.49
60	12.04	13.38	0.6	0.61
Mean	**15.75**	**13.80**	—	**0.70**
70	19.35	16.01	1.0	0.78
80	24.86	19.93	1.2	1.02
90	40.61	26.36	1.8	1.46
95	50.62	32.42	2.4	1.98
97.5	95.60	39.50	4.0	2.62
Maximum	146	109	5.0	9.36

[a] Level corresponds to estimated 1/1000 lifetime risk of fatal lung cancer and 1/100 risk of fatal heart disease.

e.g., on the distribution of values for offices, and assumptions had to be made. Our assumptions are explained in greater detail in the Appendix. Note also that

Table III. Calculated[41] Parameter Contribution to Variance (Spread) of $\{S\}$ and $\{N_{8\text{-TWA}}\}$ in the Monte Carlo Analysis: The Biological Parameters α, δ, ϕ, γ, and ρ Contribute About 40% to the Variance

Parameter	$\{N\}$	$\{S\}$
C_v	38.5	22.2
r	20.7	13.2
G_N	17.8	9.8
P_s	10.3	5.1
d_p	8.9	6.3
q	3.7	2.3
γ	—	12.4
δ	—	11.0
α	—	9.5
ρ	—	3.9
ϕ	—	3.7
H	—	0.4
Total	100%	100%

because n_s and V are correlated parameters, they were redefined for the probabilistic model such that $n_s/V = P_s d_p$, where P_s is the smoking prevalence and d_p is the office person density. A large number of trials (10,000) were generated to minimize the effect of random variability.

6. MONTE CARLO SIMULATION RESULTS

The office air nicotine levels calculated are uniformly diluted average levels for an 8-hr office workshift, while the salivary cotinine values calculated represent daily averages assuming 7 hrs of exposure to the average office air nicotine concentration.

Nicotine. The simulation, based upon 10,000 trials, predicts a roughly lognormal distribution of nicotine concentrations $\{N_{8\text{-TWA}}\}$ for the typical office workplace (Fig. 1), in reasonable agreement (values rounded) with Hammond *et al.*'s[21] $\{N_{8\text{-WA}}\}$ office concentration results as shown in Table II [predicted vs observed]: 10th percentile [4.5 μg/m³ vs. 0.70 μg/m³], median [11 μg/m³ vs. 9.7 μg/m³cb, mean [14 μg/m³ vs 16 μg/m³], 90th percentile [26 μg/m³ vs. 41 μg/m³]. Under the model assumptions, about 58% of the variation in $\{N_{8\text{-TWA}}\}$ is contributed by parameters affecting the nicotine emission rate and smoker density, while 42% is due to air exchange rate variation (see Table III).

Cotinine. The simulation, based upon 10,000 trials, predicts a roughly lognormal distribution of salivary cotinine concentrations $\{S\}$ for typical office workers (Fig. 2), in good agreement with the observations of Emmons *et al.*[15] for nonsmoking office workers' salivary cotinine distributions: Nonsmoking workers' $\{S\}$ concentration

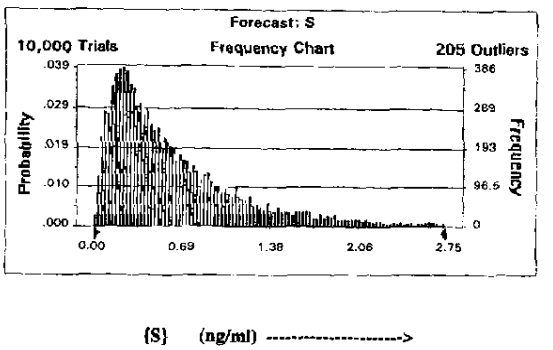

Fig. 2. Monte Carlo simulation of the expected salivary cotinine frequency distribution for U.S. nonsmoking office workers generated from the pharmacokinetic model described in Eq. (9) using 10,000 random samples from the parameter distributions described in Table I. This distribution is derived from the nicotine distribution shown in Fig. 1, assuming one worker is "sampled" per office. The median value is 0.49 ng/ml, the mean value is 0.70 ng/ml, and the range is 0.01–9.4 ng/ml. (N.B.: "Outliers" refers to the data points beyond the display range.)

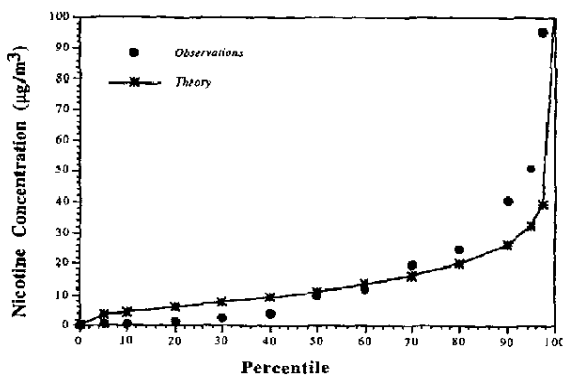

Fig. 3. Air nicotine: Theory vs. observations. Plot of measured (n = 61) nicotine concentration (solid circles) by distribution percentile for nine Massachusetts office workplaces with unrestricted smoking (Data from Hammond *et al.*)[21] vs. Monte Carlo simulation (n = 10,000) of nicotine concentration expected for a "typical" office workplace using the model based on Eq. (5) (solid line with crosses). The observational data were taken for 7 days (averaging over periods of nonoccupancy) and scaled to an 8-hr workday. The simulated $N_{8\text{-TWA}}$ data were calculated for an 8-hr workday.

as shown in Table III: [predicted vs observed]: 10th percentile [0.14 ng/ml vs not reported], median [0.49 ng/ml vs. 0.50 ng/ml], mean [0.70 ng/ml vs. not reported], 90th percentile [1.5 ng/ml vs. 1.8 ng/ml]. Under the model's assumptions, about 60% of the variation in $\{S\}$ is due to variation in parameters determining the nicotine exposure, while about 40% is due to biological variation in nicotine absorption and cotinine metabolism (see Table III).

The mean and percentiles under 50% could not be calculated for the Emmons *et al.* data because 0.5 ng/ml was the limit of detection. It should also be noted that the nonsmokers defined as exposed "at work only" (i.e., at work but not at home) in the Emmons study may have had other nonhome sources of ETS exposure contributing to their salivary cotinine levels. Since the predicted distribution is for 10,000 workers, and the observations are for 89, and given that background is not included, the differences are small and in the right direction, with the predicted values below the observed, allowing for a small nonworkplace (and nonhome) background; the agreement appears reasonable. A linear regression of $\{S\}$ in ng/ml vs. $\{N\}$ in μg/m³ for the 10,000 trials yields a slope $S/N = 0.05$.

7. DISCUSSION

In probablistic form, the models given here are able to explain by percentile the shape of the observed exposure distribution of nicotine in the air of nine Massachusetts workplaces with unrestricted smoking, as shown in Fig. 3, and the observed dose distribution of salivary cotinine in 89 nonsmoking Rhode Island white collar workers who reported being exposed to ETS only at work, as shown in Fig. 4. Cigarette smoking prevalence (all ages) in these two neighboring states is similar to the average for all states.[51] The close agreement between model and observations (Figs 3 and 4, Table II) suggests that the models we have developed for nicotine and cotinine incorporate the parameters necessary and sufficient for their prediction.

With respect to the simulated salivary cotinine distributions, it must be noted that the Monte Carlo analysis we conducted simulates one worker salivary cotinine level for each office nicotine value. In deriving a composite salivary cotinine distribution, the actual number of nonsmoking workers at each exposure level is not known. Therefore, we must assume that the salivary cotinine levels as simulated are representative of all U.S. office workers in offices with unrestricted smoking.

While the simulated distributions agree reasonably well with independent observations, it is important to recognize the uncertainties in the parameter values of the model. The distributions for the physiological parameters are based upon experimental and observational data; however, some of the datasets are very limited. The smoking prevalence and smoking rates are based on

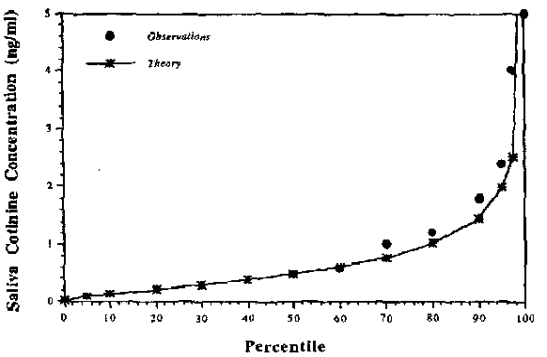

Fig. 4. Salivary cotinine: Theory vs. observations. Measured salivary cotinine concentration (solid circles) by percentile for 89 Rhode Island workers who reported exposure to ETS at work only (Data from Emmons *et al.*[15]; K. M. Emmons, personal communication) plotted vs. Monte Carlo simulation of cotinine concentration using the model based on Eq. (9) (solid line with crosses). The model assumes 7-hr of exposure to $N_{8\text{-TWA}}$ per 8-hr workday.

large surveys, and the means are expected to be generally representative, although the full distributions are uncertain. The mean values for C_v and q are also based on empirical evidence, although the full distributions are similarly uncertain. The nicotine emission per cigarette is not sales-weighted; therefore there is some uncertainty in extrapolating these results. The distributions for duration of exposure (i.e., length of workday) and office person density are unknown; however, reasonable assumptions can be inferred.

Our simulation (see Table I equations) does not explicitly contain the distribution of office volumes;[28] rather, the Monte Carlo analysis relies on the smoker density parameter, $n_s/V = d_p P_s$ which is calculated as the product of the number of persons per unit volume times the smoker prevalence and is expected to be more stable. A complexity that can occur for small offices is the impact of "fractional smokers" generated by the simulation, although this is expected to average out over a large number of offices. In large offices, the effect of fractional smokers would be minimal.

Despite the unavoidable uncertainties in some of the parameter distributions, our simulated results agree reasonably well with available real world data, suggesting that the model structure and the mean values are fairly sound. Although the model validation is limited, our results appear to predict the midranges of the air nicotine and salivary cotinine distributions well. The extreme values, particularly those at the upper end of the distributions, have greater uncertainty and are less stable. We appear to be underpredicting the variability of N; however, it is unknown which parameter variabilities are under estimated. The values for nicotine means for the point-estimate model and the simulation are, respectively (for $N_{8\text{-TWA}}$), 11.2 μg/m³ vs. 13.8 μg/m³. The $S/N_{8\text{-TWA}}$ ratio is the same in both cases, 0.05 ng/ml per μg/m³. However, as Figs. 3 and 4 show, the simulations allow a much more thorough comparison with the observed data than do the point-estimate models.

These results suggest, contrary to the speculation by Idle,[49] that salivary cotinine as a quantitative indicator of ETS exposure is not "seriously compromised" by individual biological variations. For simplicity in estimating concentrations, the nicotine Eq. (1) can be expressed as $N \approx 1600\ d_p P_s/C_v$, and Eq. (5) as $N_{8\text{-TWA}} \approx 1300\ d_p P_s/C_v$ in units of μg/m³. Similarly, the salivary cotinine equation can be expressed in the simplified form $S = 0.05\ N_{8\text{-TWA}}$, in units of ng/ml, where ETS exposure is assumed to occur for 7 hrs/day.

8. ESTIMATED MORTALITY ASSOCIATED WITH ETS NICOTINE AND SALIVARY COTININE

We now use our pharmacokinetic model for salivary cotinine to assess the risk of disease at various levels of dose using a dose-response relationship and to assess the gravity of that risk, employing decision rules in use by federal environmental and occupational health regulatory agencies.

Dose–response. Repace and Lowrey[3] developed a pharmacokinetic risk model which enables nicotine in air and cotinine in plasma and urine to be related to lung cancer risk from passive smoking. The risk model on which this was based was successful in predicting the risk ratio observed in the American Cancer Society (ACS) Cohort Study of passive smoking and lung cancer in nonsmokers in the ACS CPS I study.[18] The model also predicted a doubling of nonsmokers' lung cancer risk due to workplace passive smoking,[50] consistent with the findings of Reynolds *et al.* discussed above.[55] Using this model, and assuming a linear dose–response relationship, Repace and Lowrey[3] associated an average plasma cotinine level of $P = 0.4$ ng/ml for 40 years with an increased lung cancer mortality risk of 1/1000. For purposes of comparison with OSHA's decision rules, we adjust this to a a 45-year working lifetime (WLT_{45}), and convert the dose–response relationship from plasma to salivary cotinine. Using Eq. (8) with $\gamma = 1.16$ yields a dose–response relationship for lung cancer which associates an average salivary cotinine level of 0.4 ng/ml

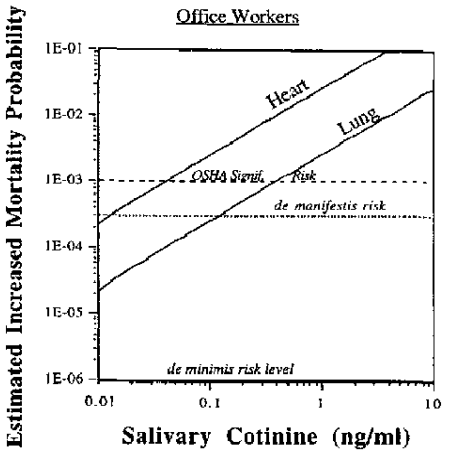

Fig. 5. Estimated increased heart disease death and lung cancer mortality risk vs. average salivary cotinine level for nonsmoking office workers from workplace ETS exposure for a 45-yr working lifetime, based on the assumption that risk is linear with dose. From Table II, >95% of office workers are estimated to exceed 0.04 ng/ml, corresponding to the OSHA *significant risk* level (1 expected death per 1000 workers at risk) for heart disease, and virtually all such workers are estimated to exceed the *de manifestis* and *de minimis* (beneath regulatory concern) risk levels for heart disease. For lung cancer, about half of office workers are estimated to have salivary cotinine concentrations exceeding 0.4 ng/ml, corresponding to the OSHA *significant risk* level; about three-fourths of office workers appear to exceed the *de manifestis* risk level, and all are estimated to exceed the *de minimis* risk level.

with a probability of lung cancer death of one excess lung cancer death per thousand workers per WLT_{45}. This risk model[3] also associates, per WLT_{45},[21] a workplace airborne nicotine concentration of 6.7 $\mu g/m^3$ to an estimated excess lung cancer risk of 1/1000 (10^{-3}).

Risk Assessment. De minimis risk, typically a 10^{-6} lifetime risk, is that level at or beneath which involuntary risk is generally of no regulatory concern, and the *de manifestis* risk, typically a 3×10^{-4} lifetime risk, is that level at or above which involuntary hazards are invariably of regulatory concern.[45] With respect to OSHA, that Agency has frequently used an increased lifetime risk of 10^{-3} due to exposure during a working lifetime as a legally defensible "Significant Risk," or regulatory action level.[2] Mapping the simulated salivary cotinine distribution in Table II into risk using this dose-response relation it is estimated that about 60% of workers in office workplaces with unrestricted smoking exceed OSHA's *significant risk* level for lung cancer. *De manifestis* risk occurs at 0.14 ng/ml, which based upon table II, would appear to be exceeded for 90% of workers. Virtually all workers would exceed the 10^{-6} *de minimis* risk level which occurs at 0.4 pg/ml. These results are summarized in Fig. 5.

A rough approximation to the risk of heart disease mortality from office passive smoking may be obtained as follows. Repace and Lowrey[66] and EPA,[1] respectively, estimated the total annual number of U.S. passive smoking lung cancer deaths (LCDs) as 5000 and 3000. Wells[63] estimated 61,000 passive smoking heart disease deaths (HDDs), Glantz and Parmley[64] 37,000 HDDs, and Steenland[65] 35,000–40,000 HDDs. If all studies are averaged, the ratio of HDDs to LCDs is 45,000/4000 ≈ 11:1., This suggests that the risk of heart disease mortality from passive smoking is about tenfold the risk of lung cancer mortality, and thus levels of salivary cotinine of 0.4 ng/ml in nonsmokers may be roughly associated with a 45-yr working lifetime heart disease risk of the order of 1/100, assuming a linear dose–response relationship. From the risk levels shown in Fig. 5, it is seen that for all cotinine levels ≥0.04 ng/ml, significant risk is exceeded for heart disease mortality. From the percentiles of the cotinine distribution in Table III, we estimate that more than 95% of nonsmoking workers exceed OSHA's *significant risk* level due to passive smoking. Similarly, virtually all workers in office workplaces with unrestricted smoking are estimated to exceed both the *de manifestis* and *de minimis* risk levels.

OSHA estimates that 74,201,000 nonsmoking adults (73.01% of the U.S. labor force) are currently employed.[2] Of these, about 54% are office workers, who work in many of the 4.5 million commercial buildings in the U.S.[17,28] In a national survey of 100,000 workers during 1992–1993 conducted by the National Cancer Institute and the Bureau of the Census, about 30% of all office workers (28% of nonsmoking workers) reported that their workplaces either had a policy which allowed smoking or had no policy on workplace smoking.[69] This suggests that 11.2 million ($0.28 \times .54 \times 74{,}201{,}000$) nonsmoking office workers have workplaces with unrestricted smoking. Using the mean combined dose-response estimated for heart disease and lung cancer, we estimate the population risk for these workers at 215,600 deaths in 45 years {0.70 ng/ml /(0.4 ng/ml/0.011 deaths per WLT) $\times$ 11.2 $\times$ 10^6 workers}, or about 4800 deaths per year in nonsmoking office workers, with about 4400 from heart disease, and about 440 from lung cancer. These estimates may be compared with OSHA's risk estimates of from 140 to 722 annual cases of fatal lung cancer and from 2094 to 13,000 deaths from heart disease per year occur among all nonsmoking U.S. workers (white-, pink-, and blue-collar), or that between 2238 and 13,722 total deaths per year will be avoided by elimination of nonsmokers' exposure to

ETS in the workplace.[2] By comparison, the estimated number of nonsmokers' lung cancer deaths annually from all passive smoking (work, home, social) is about 4000 (compared to a total from all causes in both smokers and nonsmokers of 139,000),[1,66] and the annual number of heart disease deaths in nonsmokers from passive smoking is estimated to be about 45,000 (compared to a total from all causes in both smokers and nonsmokers of 537,000).[63]

9. CONCLUSIONS

We have developed models for estimating ETS air nicotine concentrations in office workplaces with unrestricted smoking based on 6 parameters, and nonsmoking workers' salivary cotinine doses based on 7 parameters, including nicotine. Using Monte Carlo simulation, we compared our model results to observed distributions of airborne nicotine in offices and on salivary cotinine levels in nonsmoking office workers, and found an adequate fit. We then used our model to derive lifetime lung cancer and heart disease mortality risk estimates from chronic workplace passive smoking as a function of salivary cotinine.

Our model results suggest that at the current 28% prevalence of unrestricted smoking in the office workplace, passive smoking creates a significant risk, causing an estimated 4000 heart disease deaths and 400 lung cancer deaths annually among nonsmoking office workers.

ACKNOWLEDGMENTS

The authors are grateful to N. Benowitz for his unpublished data and to S. A. Glantz for helpful discussions.

APPENDIX: PARAMETER VALUES FOR THE MODEL

Table 1 summarizes the means, standard deviations, and ranges for the parameters. The mean values from the literature are used as target means in the Monte-Carlo simulation program,[41] In general, a standard deviation of 20% was used for parameters for which there were fairly good data, and 30% was used when the data were limited, while 15% was used when a tighter distribution was anticipated, and 50% was used for parameters that were highly variable or uncertain.

1. γ, the salivary-to-plasma cotinine ratio: the following means and standard deviations for (S, P) pairs were reported[12,70]: $S = 1.69 \pm 2.27$ ng/ml and $P = 1.46 \pm 2.28$ ng/ml, for 100 persons exposed to passive smoking, yielding $\gamma = 1.16$. For five persons exposed to oral nicotine,[35] $\gamma = 1.19$. For nine persons exposed to oral and intravenous dosing of cotinine,[11] $\gamma = 1.28 \pm 0.1$ (mean and SD). We assume a mean and standard deviation of $\gamma = 1.16 \pm 0.35$ (30% SD) normally distributed.

2. δ, the cotinine plasma clearance rate (ml/min): from DeSchepper *et al.* (1987)[71] ($n = 4$), the mean and standard deviation is $\delta = 60.7 \pm 9.9$ ml/min. From Curvall *et al.* (1990), assuming a 70 kg person, based on oral and IV dosing of cotinine[11] ($n = 9$), $Cl_T = 61.4 \pm 7.1$ ml/min. A weighted average of the two results yields $\delta = 61.2 \pm 8$ ml/min (mean and SD), normally distributed; we assume $\delta = 61 + 18$ (30%).

3. ϕ, the nicotine-to-cotinine conversion efficiency (dimensionless): Benowitz (personal communication) reports: $\phi = 0.78$ median and mean, ± 0.10 SD, i.e., normally distributed ($n = 146$) range, 0.49–1.0, coefficient of variation 13%, using intravenous infusion of nicotine, with no significant difference between smokers and nonsmokers. We assume a mean and SD for $\phi = 0.78 \pm 0.16$ (20%), normally distributed, but truncated such that ϕ does not exceed 1.

4. α, the lung nicotine absorption efficiency was measured[47] with a mean and SD for $\alpha = 0.713 \pm 0.102$, ($n = 17$), range 45–95%. We assume $\alpha = 0.71 \pm 0.21$ (30%), normally distributed but truncated such that $\alpha \leq 1$.

5. C_v is the air exchange rate due to mechanical ventilation and infiltration. The basic design standard for North American ventilation rates is the ASHRAE Standard.[7] Persily[25] reported on annual average air exchange rates in 14 large U.S. office buildings constructed between 1969 and 1984 (V = 18,500 m^3 to 249,000 m^3). Omitting two buildings with unusual characteristics, data presented for the remaining 12 buildings had a mean and SD for $C_v = 0.84 \pm 0.25$ ach and a median of 0.80 ach. 0.84 ach is the expected value for the ASHRAE Standard for offices.[25,60] Air exchange rates ranged as low as 0.2 ach (2% of measurements) with few measurements above 3.5 ach. The combined distribution of buildings exhibited a lognormal distribution of air exchange rates. We take C_v to be lognormal, with

bounds of 0.2 to 8 air changes per hour (ach), and a mean value of 0.84 ach as calculated above, corresponding to the ASHRAE Standard. We assume a standard deviation of 0.42 ach (50%).

6. $q = C_{eff}/C_v$. q is the ratio of the effective ventilation rate C_{eff}, to the mechanical ventilation rate C_v. ETS RSP and nicotine are adsorbed onto surfaces, which enhances their removal relative to that for nonreactive contaminants which occurs by ventilation only. At the mixing extremes, turbulent to stable, q might vary from 1 to 4, but field experiments in commercial buildings suggest[4,58] a relatively stable value of about 2.2, independent of C_v. Rickert *et al.*[46] affirmed this hypothesis using controlled experiments. We assume that $q = 2.2$, is lognormally distributed, and ranges between 1 and 4, with a standard deviation of 15%.

7. G_N, the ETS-nicotine emission factor. In earlier work, this emission factor was estimated from the expression $G_N = G_R/10$,[3,8,9,19] yielding a value of 2.4 mg/cig. Data comparing ETS-RSP emissions to ETS-nicotine emissions for the top 50 U.S. cigarette brands, smoked by smokers in an unventilated chamber, and stated to represent 64% of the U.S. market, was submitted to OSHA by RJR.[27,29] From this data, we calculate a mean and SD for G_N = 1765 ± 282 μg/cig (range 1100–2600 μg/cig), and an ETS RSP-to-Nicotine ratio of 7.9 ± 1.6.[50] An analysis[30,69] shows that nicotine is normally distributed, that RSP is fairly normal, and that the RSP-to-nicotine ratio is normally distributed. Leaderer and Hammond[9] measured the ETS-RSP emissions for ten brands of cigarettes representing 48% of the U.S. market, as well as the RSP/nicotine ratio (14:1) in the steady state. Dividing the RSP emissions by this ratio, we estimate the nicotine emissions, using 0.63 g of tobacco per cigarette. The results yield an estimated 1.23 ± 0.20 mg/cig for ETS nicotine emissions. In several field studies, RSP to nicotine ratio ranged from 8.6 to 10.8, averaging about 10.[9] For 10:1 the estimated nicotine yield averages 1.7 mg/cig, close to the value calculated from the RJR data. We assume a mean and SD for G_N = 1800 ± 540 (30%), range 700–2900, to allow for partially-smoked cigarettes at the low end, and slightly higher to allow for cigarettes which are smoked down to the filter. We also give a larger variability than derived from the RJR results to allow for the fact that the data are not identified by brand, and therefore cannot be sales-weighted.[52]

8. ρ, the respiration rate. The respiration rate for a resting person is about 0.36 m³/hr, for a person sitting about 0.60 m³/hr, for alternate sitting and light work, about 0.99 m³/hr, for light work about 1.47 m³/hr, and for heavy work, about 2.04 m³/hr.[48] We assume that office workers have an average respiration rate of 0.9 m³/hr, to reflect more sitting than light work, normally distributed, and bounded between 0.4 and 1.4, with a standard deviation of 0.18 m³/hr (20%).

9. P_s, the smoking prevalence. We assume a smoking prevalence of 29% using national statistics.[23] The office smoking prevalence is assumed to bounded between 5–90%, normally distributed, with a default standard deviation of 0.06 (20)%. White collar workers have a lower smoking prevalence than blue collar or service (pink collar) workers, who may also be present in some buildings containing offices.[43]

10. $d_p = (n_p/V)$, the person density, is assumed to vary normally, and to be bounded between 0.005 persons per m³ to 0.08 persons per m³, with a mean value of 0.025, and a default standard deviation of 0.005 (20%). The mean value is based upon an assumed net mean office occupancy of seven persons per thousand square feet of office space in keeping with the default assumption of the ASHRAE Standard, and assumes a 10-ft ceiling.

11. H, the number of hours of exposure of the nonsmokers per full-time workshift. The mean value is set at 7, and the possible range is taken to be 6–8, with a standard deviation of 0.5, normally distributed. The length of the workshift is kept tight because if is calculated specifically for an 8-hr workshift with 1 h (unexposed) for lunch (see below).

12. r, the smoking rate is assumed to vary from 0.1 cig/sm-hr to 6 cig/sm-hr, with an average of 2,[62] and a standard deviation of 0.6 (30%).

13. τ, is the averaging time over which the dose is calculated. We calculate a daily average by setting τ = 1440 min/day.

14. $f = N_{ave}/N$ is the ratio of the time-weighted average N_{ave} of a concentration $N(t)$ over a period ΔT = 8 hrs to the equilibrium concentration N, where the duration of smoking is t_s = 7 hr. The time weighted integrals of this distribution can be represented, for a 3 hr AM growth period followed by a 1 hr lunch break decay period followed by a 4 hr PM growth period, by the expression $f = \{7/8 + (-1 + e^{-4qCv}$

$- e^{-5qC_v} + e^{-8qC_v})/8qC_v\}$, where the total length of the workday is 8 hr. For $q = 2.2$, and $C_v = 0.84$ hr^{-1}, $f = 0.81$; as C_v varies from 0.2 to 10 ach, f varies from 0.62 to 0.87. This expression may also be written in simplified form using curve-fitting, as $f = 0.86 - 0.39e^{-2.6C_v}$. Methods of calculating N_{ave} are discussed elsewhere.[36]

REFERENCES

1. U.S. Environmental Protection Agency, Washington, D.C. 20460, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders" (EPA 600/6-90/006F) (1992).
2. U.S. Dept. of Labor, Occupational Safety & Health Administration, 29 CFR Parts 1910, 1915, 1926, and 1928 Indoor air quality, proposed rule Fed Reg 59 #65, Tues. (April 5, 1994), pp. 15968–16039.
3. J. L. Repace and A. H. Lowrey, "An Enforceable Indoor Air Quality Standard for Environmental Tobacco Smoke in the Workplace," *Risk Anal.* **13**, 463–475 (1993).
4. J. L. Repace, "Indoor Concentrations of Environmental Tobacco Smoke: Models Dealing with Effects of Ventilation and Room Size," in I. O'Neill, K. Brunnemann, B. Dodet, and D. Hoffmann, eds., *IARC Scientific Publications no. 81, Environmental Carcinogens—Selected Methods of Analysis—Volume 9, Passive Smoking*, Chap. 3 (International Agency for Research on Cancer, World, Health Organization, United Nations Environment Programme, Lyon, France, 1987).
5. B. Leaderer, "Assessing Exposures to Environmental Tobacco Smoke," *Risk Anal.* **10**, 19–26 (1990).
6. J. L. Repace and A. H. Lowrey, "Tobacco Smoke, Ventilation, and Indoor air Quality," *ASHRAE Trans.* **88**, 894–914 (1982).
7. ASHRAE STANDARD 62-1989, "Ventilation for Acceptable Indoor Air Quality," The American Society of Heating, Refrigerating, and Air Conditioning Engineers, Inc., Atlanta.
8. J. M. Daisey, K. R. R. Mahanama, and A. T. Hodgson, "Toxic Volatile Organic Compounds in Environmental Tobacco Smoke: Emission Factors for Modeling Exposures of California Populations," Final Report, California Air Resources Board, Sacramento, CA (Oct. 1994).
9. B. P. Leaderer and S. K. Hammond, "An Evaluation of Vapor-Phase Nicotine and Respirable Suspended Particle Mass as Markers for Environmental Tobacco Smoke," *Environ. Sci. Technol.* **25**, 770–777 (1991).
10. National Research Council, *Environmental Tobacco Smoke—Measuring Exposures and Assessing Health Effects* (National Academy Press, Washington, D.C., 1986).
11. M. Curval, C. E. Elwin, E. Kazemi-Vala, C. Warholm, and C. R. Enzell, "The Pharmacokinetics of Cotinine in Plasma and Saliva from Nonsmoking Healthy Volunteers," *Eur. J. Clin. Pharmacol.* **38**, 281–287 (1990).
12. M. J. Jarvis, "Application of Biochemical Intake Markers to Passive Smoking Measurement and Risk Estimation," *Mutat. Res* **222**, 101–110 (1989).
13. J. L. Repace, "Dietary Nicotine Won't Mislead on Passive Smoking," *Brit. Med. J.* **308**/6920, 61–62 (Jan. 1, 1994).
14. M. J. Jarvis, "Unless Subjects Eat 90 kg Tomatoes a Day," *Brit. Med. J.* **308**/6920, 62 (Jan. 1, 1994).
15. K. M. Emmons, D. B. Abrams, R. Marshall, B. H. Marcus, M. Kane, T. E. Novotny, and R. A. Etzel "An Evaluation of the Relationship Between Self-Report and Biochemical Measures of Environmental Tobacco Smoke Exposure," *Prevent. Med.* **23**, 35–39 (1994).
16. R. Etzel, "A Review of the Use of Saliva Cotinine as a Marker of Tobacco Smoke Exposure," *Prevent. Med.* **19**, 190–197 (1990).
17. U.S. Bureau of the Census, *Statistical Abstracts of the United States, 1993*, 113th Ed. (Washington, D.C., 1993).
18. J. L. Repace and A. H. Lowrey, "A Quantitative Estimate of Nonsmokers' Lung Cancer Risk from Passive Smoking," *Environ. Int.* **11**, 3–22 (1985).
19. J. L. Repace and A. H. Lowrey, "A Rebuttal to Tobacco Industry Criticism of An Enforceable Indoor Air Quality Standard for Environmental Tobacco Smoke," *Risk Anal.* **15**, 7–13 (1995).
20. E. T. H. Fontham, P. Correa, P. Reynolds, A. Wu-Williams, R. S. Greenberg, P. A. Buffler, S. D. Greenberg, V. W. Chen, T. Alterman, P. Boyd, D. F. Austin, and J. Liff, "Environmental Tobacco Smoke and Lung cancer in Nonsmoking Women: A Multicenter Study," *JAMA* **271**, 1752–1759 (1994).
21. S. K. Hammond, G. Sorensen, R. Youngstrom, and I. K. Ockene, "Occupational Exposure to Environmental Tobacco Smoke," *JAMA* **274**, 956–960 (1995).
22. W. Ott, L. Langan, and P. Switzer, "A Time Series Model for Cigarette Smoking Activity Patterns: Model Validation for Carbon Monoxide and Respirable Particles in a Chamber and an Automobile," *J. Exp. Anal. Environ. Epidemiol.* (Suppl. 2):175–200 (1992).
23. Trends in cigarette smoking prevalence (%) by sex and by race—United States, ages 18+, 1995–1991, Users of Tobacco Products—United States, Ages 18+, 1991, Trends in the number of adults by cigarette smoking status, overall and by sex, race, Hispanic origin, age and education—Source: National Health Interview Surveys, (1965–1991, compiled by the Office on Smoking and Health, Centers for Disease Control and Prevention, Atlanta, GA. (personal communication).
24. W. R. Ott, *Environmental Statistics and Data Analysis* (Lewis Publishers, Boca Raton, FL, 1995).
25. A. Persily, Ventilation Rates in Office Buildings, Proc. ASHRAE Conference IAQ '89, San Diego, CA (1989).
26. E. T. H. Fontham, P. Correa, A. Wu-Williams, P. Reynolds, *et al.* "Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study," *Cancer Epidemiol. Biomarkers Prev.* **1**, 35–43 (1991).
27. Testimony of P. Nelson, R. J. Reynolds Tobacco Company, OSHA Docket #H-122, comment 8-266, Indoor Air Quality Proposed Rule, U.S. Occupational Safety & Health Administration, Washington, D.C.
28. *Statistical Abstracts of the United States 1993*, 113th Ed., Table 1253, Commercial Buildings and Workers—Selected Building Characteristics by floorspace: 1989, U.S. Dept. of Commerce, Bureau of the Census, Washington, D.C. (1993).
29. P. R. Nelson, P. Martin, M. W. Ogden, D. J. Heavner, C. H. Risner, K. C. Maiolo, P. S. Simmons, and W. T. Morgan, "Environmental Tobacco Smoke Characteristics of Different Commercially Available Cigarettes," Proc. 4th International Aerosol Conf., Los Angeles, CA (1994).
30. A. Tsang and N. Klepeis, "Analysis of RSP vs Nicotine for 51 Cigarettes," Data from OSHA Indoor Air Docket H-122 comment #8-266, submitted by P. R. Nelson of the R. J. Reynolds Tobacco Company (personal communication, 1994).
31. W. Ott, P. Switzer, and J. Robinson, "Particle Concentrations Inside a Tavern Before and After Prohibition of Smoking: Evaluating the Performance of an Indoor Air Quality Model," *J. Air Waste Manage. Assoc.* **46**, 1120–1134 (1996).
32. American Heart Association Medical/Scientific Statement, Position Statement Environmental Tobacco Smoke and Cardiovascular Disease—A position paper from the council on cardiopulmonary and critical care, American Heart Association, A. E. Taylor, D. C. Johnson, and H. Kezemi, American Heart Association, Circulation, vol. 86, pp. 1–4 (1992).
33. Testimony of the Phillip Morris Tobacco Company, OSHA Proposed Indoor Air Rule, Docket #51, Testimony of the R.J. Reyn-

olds Tobacco Company, OSHA Proposed Indoor Air Rule, Docket #H-122, Before the Occupational Health and Safety Administration, U.S. Department of Labor, Washington, D.C. 20210 (1994).
34. J. L. Pirkle, K. M. Flegal, J. T. Bernert, D. J. Brody, R. A. Etzel, and K. R. Maurer, "Exposure of the Population to Environmental Tobacco Smoke: The Third National Health and Nutrition Examination Survey, 1988 to 1991," *JAMA* **275**, 1233–1240 (1996).
35. M. J. Jarvis, M. A. H. Russell, N. L. Benowitz, and C. Feyerabend, "Elimination of Cotinine in Body Fluids: Implications for Noninvasive Measurement of Tobacco Smoke Exposure," *AJPH* **78**, 696-698 (1988).
36. J. L. Repace, W. R. Ott, and N. R. Klepeis, "Mathematical Models for Predicting Time-Averaged Environmental Tobacco Smoke Concentrations" *J. Exp. Anal. and Environ. Epidemiol.* (in press.)
37. J. Coghlin, S. K. Hammond, and P. H. Gann, "Development of Epidemiologic Tools for Measuring Environmental Tobacco Smoke Exposure," *Am. J. Epidemiol.* **130**, 696–704 (1989).
38. D. B. Abrams, M. J. Follick, L. Biener, K. B. Carey, and J. Hitti, "Saliva Cotinine as a Measure of Smoking Status in Field Settings," *Am. J. Publ. Health* **77**, 846–848 (1987).
39. N. L. Benowitz, "Cotinine as a Biomarker of Environmental Tobacco Smoke Exposure," *Epidemiol. Rev.* **18**, 188–204 (1996).
40. N. L. Benowitz, "The Use of Biologic Fluid Samples in Assessing Tobacco Smoke Consumption," National Institute on Drug Abuse Research Monograph Series 48—Measurement in the analysis and treatment of smoking behaviour, J. Grabowski, and C. S. Bell, eds. (DHHS, 1983).
41. Crystal Ball®, version 4.0, Forecasting and Risk Analysis for Spreadsheet Users, Decisioneering Inc., Denver, CO (1993).
42. F. de Waard, J. M. Kemmeren, L. A van Ginkel, and A. A. M. Stolker, "Urinary Cotinine and Lung Cancer Risk in a Female Cohort," *Brit. J. Cancer* **72**, 784–787 (1995).
43. Surgeon General, *Reducing the Health Consequences of Smoking. 25 Years of Progress* (U.S. Dept. of Health and Human Services, Rockville, MD, 1989).
44. Y. He, T. H. Lam, L. S. Li, R. Y. Du, G. L. Jia, *et al.* "Passive Smoking at Work as a Risk Factor for Coronary Heart Disease in Chinese Women Who Have Never Smoked," *BMJ* **308**, 380–384 (1994).
45. C. C. Travis, S. A. Richter, E. A. C. Crouch, R. Wilson, and E. D. Klema, "Cancer Risk Management," *Environ. Sci. Technol.* **21**, 415–420 (1990).
46. W. S. Rickert, J. C. Robinson, and N. E. Collishaw, "A Study of the Growth and Decay of Cigarette Smoke NO^x in Ambient Air Under Controlled Conditions," *Environ. Int.* **13**, 399–408 (1987).
47. A. Iwasi, A. Miyoji and S. Kira, "Respiratory Nicotine Absorption in Non-smoking Females During Passive Smoking," *Int. Arch. Occup. Environ. Health* **63**, 139–143 (1991).
48. P. L. Altman, and D. S. Ditmer, *Respiration and Circulation* (Federation of American Societies for Experimental Biology, Bethesda, MD, 1971).
49. J. R. Idle, "Titrating Exposure to Tobacco Smoke Using Cotinine—A Minefield of Misunderstandings," *J. Clin. Epidemiol.* **43**, 313–317 (1990).
50. J. L. Repace, EPA Post-Hearing Comments for the OSHA Indoor Air Rulemaking, Memorandum to S. Bayard, Submitted to OSHA Indoor Air Docket with Comments of S. Bayard, (Feb. 9, 1996).
51. Centers for Disease Control and Prevention, State Tobacco Control Highlights 1996, Office of Smoking and Health, Atlanta, GA (1996).
52. The Maxwell Consumer Report, 4th Quarter and Year-End 1994 Sales Estimates for the Cigarette Industry, Wheat First Butcher Singer Securities (February 21, 1995).
53. Surgeon General, *The Health Consequences of involuntary smoking*. (U.S. Dept. of Health & Human Services, Washington, DC., 1986).
54. H. Tunstall-Pedoe, C. A. Brown, M. Woodward, and R. Tavendale, "Passive Smoking by Self-Report and Serum Cotinine and the Prevalence of Respiratory and Coronary Heart Disease in the Scottish Heart Study," *J. Epidemiol. Commun. Health* **49**, 139–143 (1995).
55. P. Reynolds, E. T. H. Fontham, P. Correa, A. Wu, P. A. Buffler, and R. S. Greenberg, "Occupational Exposure to Environmental Tobacco Smoke," *JAMA* **275**, 441–442 (1996).
56. J. L. Repace and A.H. Lowrey, "Predicting the Lung Cancer Risk of Domestic Passive Smoking," *Am. Rev. Resp. Dis.* **136**, 1308 (1987).
57. K. M. Emmons, D. B. Abrams, R. J. Marshall, R. A. Etzel, T. E. Novotny, B. H. Marcus, and M. E. Kane, "Exposure to Environmental Tobacco Smoke in Naturalistic Settings," *Am. J. Pub. Health* **82**, 24–28 (1992).
58. B. P. Leaderer, W. S. Cain, R. Isseroff, and L. G. Berglund, Paper 81-22.6, Proc 74th Annual Mtg. of the Air Pollut. Control Assoc., Philadelphia (1981).
59. B. P. Leaderer, W. S. Cain, R. Isseroff, and L. G. Berglund, "Ventilation Requirements in Buildings: II. Particulate Matter and Carbon Monoxide from Cigarette Smoking," *Atmos. Environ.* **18**, 99–106 (1984).
60. J. L. Repace and A. H. Lowrey, "An Indoor Air Quality Standard for Ambient Tobacco Smoke Based on Carcinogenic Risk," *NYJM* **85**, 381–383 (1985).
61. M. C. Marbury, S. K. Hammond, and N. J. Haley, "Measuring Exposure to Environmental Tobacco Smoke in Studies of Acute Health Effects," *Am. J. Epidemiol.* **137**, 1089–1097 (1993).
62. J. L. Repace and A. H. Lowrey, "Indoor Air Pollution, Tobacco Smoke, and Public Health," *Science* **208**, 464–474 (1980).
63. A. J. Wells, "Passive Smoking as a Cause of Heart Disease," *JACC* **24**, 546–554 (1994).
64. S. A. Glantz and W. W. Parmley, "Passive Smoking and Heart Disease: Epidemiology, Physiology, and Biochemistry," *Circulation* **83**, 1–12 (1991).
65. K. Steenland, "Passive Smoking and Risk of Heart Disease," *JAMA* **267**, 94–99 (1992).
66. J. L. Repace and A. H. Lowrey, "Risk Assessment Methodologies in Passive Smoking-Induced Lung Cancer," *Risk Anal.* **10**, 27–37 (1990).
67. Surgeon General, *The Health Consequences of Involuntary Smoking* (U.S. Dept. of Health & Human Services, Washington, D.C., 1986).
68. National Institute for Occupational Safety and Health, Current Intelligence Bulletin #54, Environmental Tobacco Smoke in the Workplace, Lung Cancer and Other Health Effects, NIOSH, Cincinnati, OH (June 1991).
69. K. K. Gerlach, D. R. Shopland, A. M. Hartman, and J. T. Gibson, and T. E. Pehacek, "Workplace Smoking Policies in the U.S.: Results from a National Survey of over 100,000 Workers," *Tobacco Cont.* (in press).
70. M. J. Jarvis, H. T. Pesoe, C. Feyerabend, L. Vesey, and Y. Saloojee, "Biochemical Markers of Smoke Absorption and Self-Reported Exposure to Passive Smoking," *J. Epidemiol. Commun. Health* **38**, 335–339 (1984).
71. P. J. De Schepper, A. Van Hecket, and J. M. Van Rossum, "Kinetics of Cotinine After Oral and Intravenous Administration to Man," *Eur. J. Clin. Pharmacol.* **31**, 583–588 (1987).
72. L. Kawachi, G. A. Colditz, E. F. Speizer, J. E. Manson, M. J. Stamfer, W. C. Willett, and C. H. Hennekens, "A Prospective Study of Passive Smoking and Coronary Heart Disease," *Circulation* **95**, 2374–2379 (1997).